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REFLEX EFFECTS OF STIMULATING BARORECEPTORS IN THE PULMONARY ARTERY

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Previous papers have described the distribution, nerve connexions and threshold of baroreceptors in the extrapulmonary parts of the pulmonary artery of the dog (Coleridge & Kidd, 1960, 1961*a*; Coleridge, Kidd & Sharp, 1961). An attempt has now been made to elicit reflex responses by stimulating part of this receptor zone.

In anaesthetized dogs a segment of the main right pulmonary artery with its nerve supply intact was converted into a closed sac (Fig. 1). The sac was then subjected to pulsatile distension by a balloon or by blood at measured pressures, and the effects on systemic arterial pressure and heart rate examined.

A preliminary account of these experiments has been published (Coleridge & Kidd, 1961*b*).

METHODS

Thirty dogs were anaesthetized with morphine sulphate (3 mg/kg subcutaneously) followed either by chloralose (0·1 g/kg intravenously) or a 1:1 mixture of Dial Compound (allobarbitone-urethane, Ciba) and sodium pentobarbitone (Nembutal, Abbott Laboratories, Ltd.) solutions 0·25 ml./kg (intravenously). A tracheal cannula was inserted and the lungs ventilated by a Starling 'Ideal' pump. The sternum was split in the mid line, and the pericardium opened to expose the pulmonary trunk.

Preparation of the pulmonary arterial sac. The animal was ventilated with 100% O_2 for several minutes. The right lung roots were ligated; the stroke of the respiratory pump was not altered. Heparin was injected intravenously (Pularin, Evans Medical Supplies, Ltd. 500 i.u./kg). A wide-bore polyvynyl tube was inserted through an incision in the anterior wall of the main pulmonary artery and tied in position; one end of the tube lay just beyond the valves, the other in the left pulmonary artery (Fig. 1). During the 25–45 sec which it took to insert this bypass tube the thoracic inferior vena cava and the origin of the main pulmonary trunk were occluded temporarily by threads, and the respiratory pump was stopped in deflation. The incision was closed with fine sutures or a clamp. Thus the total output of the right ventricle was now carried through the bypass tube to the left pulmonary artery, and only the left lung was ventilated.

In preliminary experiments the sac was distended by a small balloon on the end of a polythene tube connected to a syringe filled with saline. The balloon was inserted into the sac through a lobar branch.

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In the majority of experiments the sac was distended with blood at measured pressures (Fig. 1, stippled circuit). Polythene tubes were tied into the central ends of three right lobar arteries and connected as shown in Fig. 1. Pulsatile distension of the sac was obtained with a pump (Coleridge & Hemingway, 1953), the outlet valve of which was removed. Mean pressure was varied by altering the height of a reservoir connected to the pump. The system was filled with heparinized blood taken from another dog. Between experiments oxygenated blood from a femoral artery was circulated through the sac and returned to a femora vein (Fig. 1). Flow and pressure in this perfusion circuit were regulated by screw clips; the circuit was closed and systemic arterial pressure allowed to stabilize before each experiment.

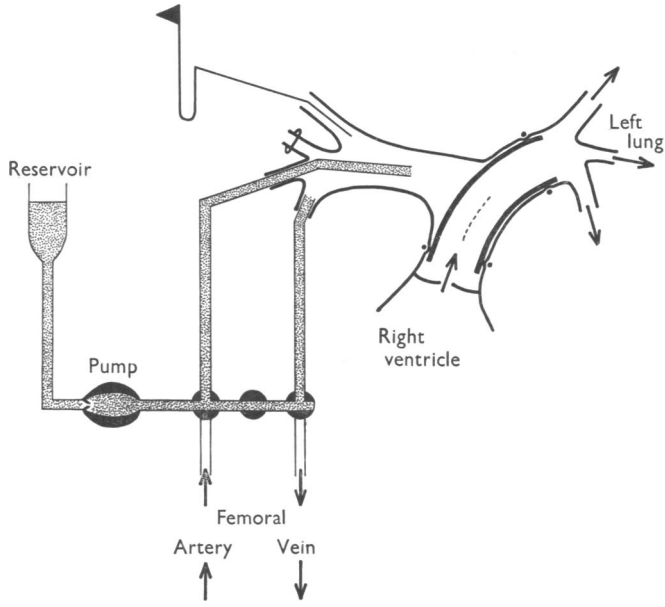

Fig. 1. Method of distending the right pulmonary arterial sac. A tube was inserted through a slit (dotted line) in the main pulmonary trunk; one end of the tube was just beyond the pulmonary valves, the other in the main left branch. The whole output of the right ventricle passed through the tube to the left lung; only the left lung was ventilated. The sac was distended with a pulsatile pressure by means of a pump (outlet valve removed) connected to two lobar arteries (stippled circuit). Mean pressure in the sac was altered by adjusting the height of a reservoir connected to the pump. Between experiments oxygenated blood was circulated through the sac from a femoral artery and returned to a femoral vein.

Recording of pressures. In different experiments the following pressures were recorded with saline or Hg manometers or with optical manometers (Coleridge & Linden, 1954): right and left atrial pressures via an external jugular and right pulmonary vein, respectively; pressure in the pulmonary arterial sac; carotid or femoral arterial pressure; respiration, from a side arm on the tracheal cannula.

Recording of action potentials. Afferent impulses were recorded from 'single fibres' dissected from the cervical vagus nerves. The effect was examined of distending the sac on the activity of the following receptors: baroreceptors in the right pulmonary arterial sac; aortic baroreceptors; right and left atrial receptors. Recording techniques and methods of

identifying different receptors have been described previously (Coleridge, Hemingway, Holmes & Linden, 1957; Coleridge & Kidd, 1960).

Fibres from receptors in the right pulmonary artery were dissected from the right vagus nerve before the sac was isolated. The bypass tube was then inserted, care being taken to avoid displacing the 'single fibre' from the electrodes. At the end of the experiment, with action potentials still being recorded from the vagal filament, the vessel was opened and explored with a fine probe to make certain that the receptor was in the wall of the sac. Fibres from receptors in other sites were dissected from the vagus nerves after the bypass tube had been inserted.

In some experiments conduction in the cervical vagus nerves was blocked by placing the nerves upon the platforms (1 cm wide) of cooling devices, the temperature of which could be varied and recorded (Coleridge *et al.* 1961).

RESULTS

In twenty-five dogs with vagus nerves intact the right pulmonary arterial sac was distended with a balloon or with blood at known pressures by means of a pump.

Distension with a balloon

In six dogs the sac was distended with a balloon filled with saline. Distension was pulsatile (approximately 30/min) with volumes of from 1 to 10 ml.

In one dog no effects were observed. In each of the other five animals distension with 1–3 ml. had no effect, but changes did occur when the distending volume was increased to 4–7 ml. In repeated tests on two of these dogs systemic arterial pressure invariably fell; in one animal, for instance, arterial pressure fell by 10–35 mm Hg in each of seven tests made over a period of about an hour. In repeated tests on each of the remaining three dogs pressure changes were more variable: arterial pressure either fell or slow rhythmical waves appeared (Mayer waves). Occasionally the fall in pressure was accompanied by brief cardiac slowing. In two dogs distension of the balloon with 8–10 ml. produced a rise of 10–15 mm Hg in systemic pressure. All the above effects were abolished by vagotomy.

Pulsatile distension with blood at known pressures

Results fell into two main groups. Distension with a pressure which was pulsatile around a mean of between 20 and 60 mm Hg produced no effect or a fall in systemic arterial pressure (group 1). By contrast, distension with a pulsatile pressure around a mean of more than 80 mm Hg almost invariably produced an increase in systemic pressure (group 2). Distension with intermediate pressures produced variable effects.

Group 1: mean sac pressure less than 60 mm Hg. In eighteen dogs with vagus nerves intact the sac was distended with pulsatile pressures around a mean of between 20 and 60 mm Hg. In eight of these animals there was

either no effect, or systemic pressure fell less than 10 mm Hg; in two dogs systemic pressure fell by more than 10 mm Hg in only one of repeated tests. Thus in ten of eighteen dogs effects were either absent, small or inconstant.

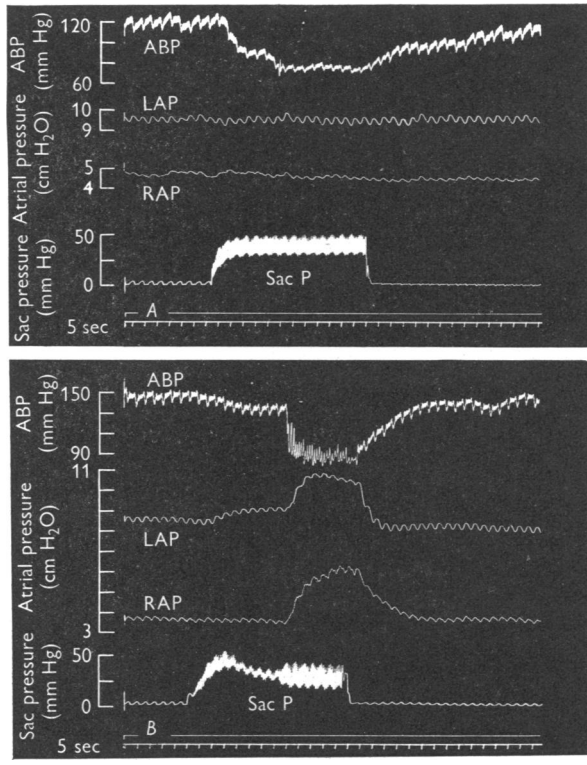

Fig. 2. Effects produced by pulsatile distension of the pulmonary arterial sac. Records *A* and *B* were made in different animals. In *B* note the marked fall in blood pressure and heart rate that occurred when the pulse pressure in the sac was increased, also the marked increase in mean atrial pressure associated with the cardiac slowing. In this and Figs. 3, 4 and 5 the following abbreviations are used: ABP, systemic arterial pressure (mm Hg); LAP, left atrial pressure (cm H_2O); RAP, right atrial pressure (cm H_2O); Sac P, pressure in pulmonary arterial sac (mm Hg).

In three or more tests on each of the remaining eight dogs distension of the sac produced a fall in arterial pressure of 10–55 mm Hg. A total of seventy-two tests were made on these eight animals: the blood pressure fell in fifty and was unchanged in twenty-two. A record of one of these experiments (Fig. 2*A*) shows a fall of about 40 mm Hg in mean systemic pressure following distension of the sac with a pulsatile pressure around a mean of 35–40 mm Hg. Sometimes, as in this experiment, systemic pressure was not restored until sac pressure was finally lowered; in other

cases systemic pressure returned towards its original level while the sac was still distended (e.g. Fig. 4*B*).

In general, large or prolonged changes in heart rate were not produced by distension of the sac. In fourteen of these seventy-two tests there was a slight and transient slowing at the beginning of distension. For instance, in one experiment a fall of 25 mm Hg in arterial pressure was maintained throughout the period of distension (75 sec), whereas an initial fall in heart rate from 182 to 150/min was maintained for only 11 sec. Pronounced bradycardia occurred in only two experiments. In

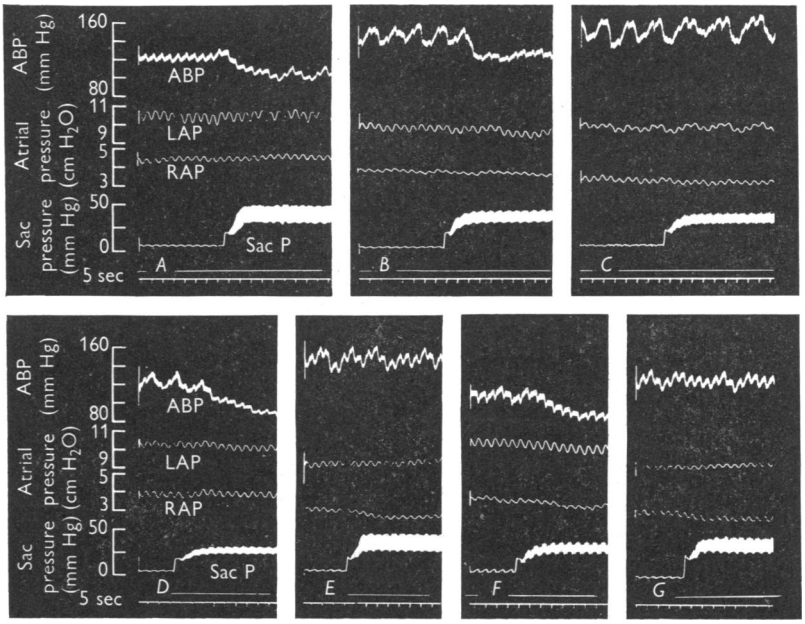

Fig. 3. Effect of cooling and section of the cervical vagus nerves on the response to pulsatile distension of the pulmonary arterial sac. Both nerves were placed upon the platforms of cooling devices the temperature of which was varied: *A*, 37° C; *B*, 11° C; *C*, 7° C; *D*, 37° C; *E*, 7° C; *F*, 37° C; *G*, 37° C. Between *F* and *G* both vagus nerves were cut. Note that vagal cooling produced Mayer waves in the systemic pressure record (*B*, *C*) which did not completely disappear when the nerves were warmed again (*D*). Abbreviations as in Fig. 2.

one of these (Fig. 2*B*) distension of the sac was followed by a fall in pressure of 10–15 mm Hg, with no change in heart rate (170/min). Pulse pressure in the sac was then increased by alteration of the pump; the heart rate fell from about 170 to 60 beats/min, and mean arterial pressure fell from about 135 to about 90 mm Hg.

The hypotension was abolished by bilateral cervical vagotomy or by cooling both vagi to 7–8° C (Fig. 3). Bradycardia was never seen after

vagotomy or vagal cooling to 7–8° C. Vagal cooling sometimes caused Mayer waves to appear in the arterial pressure record. Consequently it might be argued that failure to obtain an effect after cooling was due to alteration in the animal's general circulatory condition rather than to interruption of a particular reflex pathway. However, the effect of distending the sac appeared to be determined by the temperature to which the nerves had been cooled and not by the presence or absence of Mayer waves. This is illustrated by the series of experiments shown in Fig. 3,

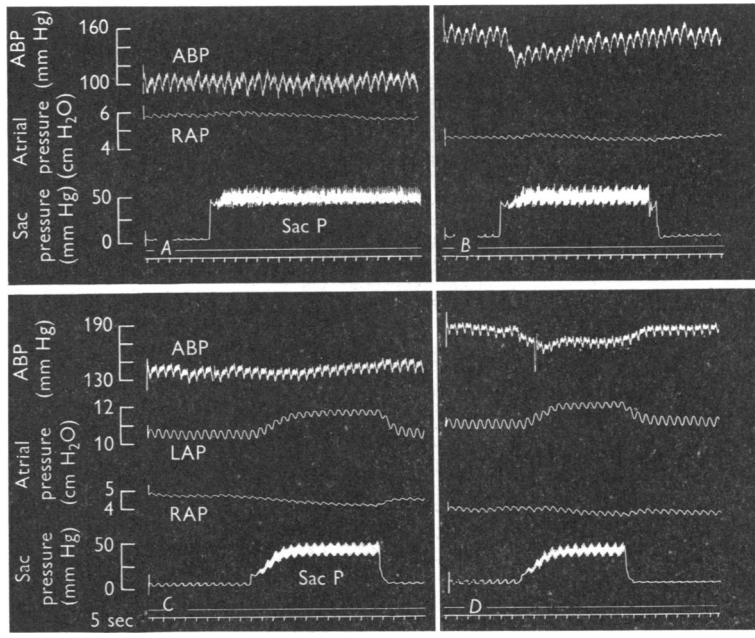

Fig. 4. Effect of occluding both common carotid arteries on the response to pulsatile distension of the pulmonary arterial sac. Records *A*, *B* and *C*, *D* were made in different animals. Abbreviations as in Fig. 2. *A*, *C* before, *B*, *D* after carotid occlusion.

in which the vagi were alternately cooled and rewarmed. Although cooling the vagi to 11° C caused the appearance of Mayer waves (*B*), the hypotensive response was not abolished until the temperature had been lowered to 7° C (*C*); and the response reappeared on warming the nerves again (*D*), even though Mayer waves were still present. On cooling again (*E*) the response was abolished; and returned once more when the nerves were warmed (*F*). The response was finally abolished by vagal section between *F* and *G*.

Distension of the sac was not followed by consistent changes in mean right or left atrial pressure, such as might be expected if the systemic

hypotension were due to an obstruction of flow into or from the right or left sides of the heart. Unless there was marked cardiac slowing (Fig. 2*B*), mean atrial pressure rarely changed by more than 1 cm H_2O, even when the sac was distended with extremely high pressures (Fig. 5). Moreover, systemic arterial pressure fell whether mean right and/or left atrial pressure increased, decreased or remained unchanged.

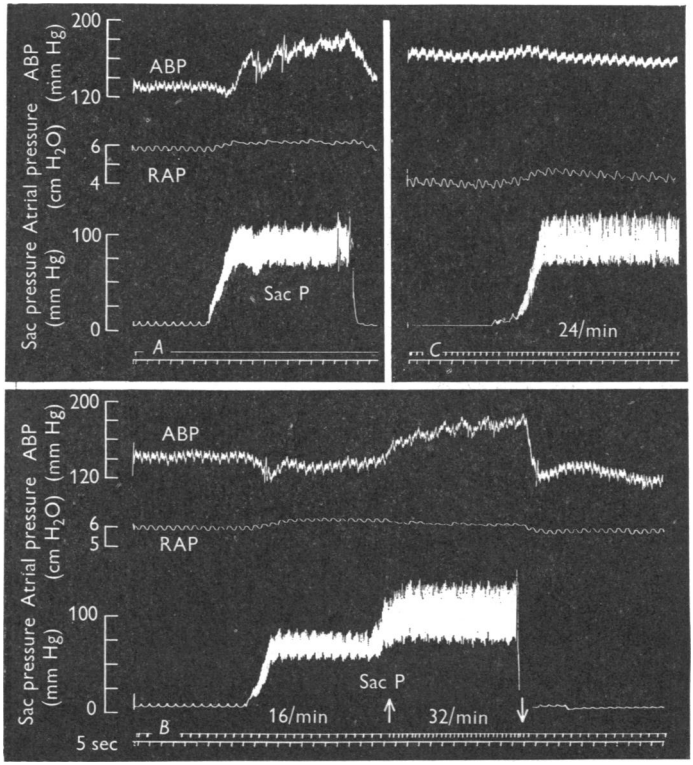

Fig. 5. Effect of distending the pulmonary arterial sac with a pressure pulse having a mean greater than 80 mm Hg. *A*, *B* with vagus nerves intact; both cervical vagi were cut between *B* and *C*. Abbreviations as in Fig. 2. In *B* and *C* respiratory movements of the chest wall and diaphragm were indicated by the signal marker (hand operated) above the time trace. In *A* the lungs were ventilated with 100% O_2; in *B* and *C* with room air. In *A* there were irregular respiratory movements (not signalled) during distension of the sac. In *B* these movements were regular and occurred at the same rate as the stroke of the respiratory pump (16/min); between the arrows the movements increased to 32/min (respiratory pump rate unchanged at 16/min). In *C* the movements remained at 24/min throughout.

Failure to obtain an effect in many of these experiments may have been due to the buffering activity of the systemic arterial baroreceptors. In six dogs, therefore, the effect of clamping the common carotid arteries was

investigated. In three animals occlusion had little or no effect on the response to distension of the sac. In the remaining three dogs arterial pressure fell in only one of sixteen tests without the carotids occluded; but it fell in sixteen of twenty-one tests when the sac was distended with both carotid arteries clamped (Fig. 4).

Group 2: mean sac pressure more than 80 mm Hg. In ten dogs with vagus nerves intact the sac was distended with a pressure which was pulsatile around a mean of more than 80 mm Hg. In twenty-eight of thirty tests on eight of these animals systemic arterial pressure increased by up to 85 mm Hg during distension. There was no effect in the remaining tests.

The response to this extreme distension of the sac is shown in Fig. 5*A*. On raising the sac pressure to a mean of just over 80 mm Hg, systemic pressure rose from about 130 mm Hg to a peak of 190 mm Hg; it fell when sac pressure was lowered. In about half of these experiments slow rhythmical waves (Mayer waves) were superimposed on the over-all increase in systemic pressure.

In six dogs systemic hypertension was accompanied by respiratory movements of the chest wall and diaphragm (Fig. 5). In Fig. 5*A* the lungs were ventilated with 100 % O_2 and small irregular respiratory movements (not recorded) were observed during distension. Ventilation was then changed to room air (*B*), and small regular respiratory movements (indicated by the signal marker) became apparent during the control period. These movements were at the same rate as the respiratory pump (16/min) but were not caused by the mechanical blast of the pump. Distension of the sac (mean pressure 65–70 mm Hg) resulted in a brief fall of about 20 mm Hg in systemic pressure, with no alteration in the respiratory movements. Pressure in the sac was then increased to a mean of 95–100 mm Hg and systemic pressure rose from about 135 mm Hg to a peak of about 180 mm Hg; and the respiratory movements increased in rate (from 16 to 32/min) and amplitude. These changes were reversed when sac pressure was lowered.

Both respiratory and blood-pressure effects could still be obtained after the vagus nerves had been cooled to 7° C. At this temperature the hypotensive response to distension with lower pressures was abolished (see group 1 above). However, the effects were always abolished by vagotomy (Fig. 5*C*).

Action potential studies

In three dogs potentials were recorded from baroreceptor fibres whose endings were situated in the right pulmonary artery between the main bifurcation and the origin of the lobar branches. The bypass tube was then inserted. All three receptors were still active after isolation of the sac, and two of them remained active for a period of 4–5 hr, during which their

response to distension was examined at intervals. Records obtained in the course of one of these experiments are shown in Fig. 6. In Fig. 6*A–C* it can be seen that impulse activity increased with pressure in the sac, and that the discharge was synchronous with the pressure pulsations in the sac and not with the animal's heart beat. This is more obvious in *D* where the rate of the pump was reduced.

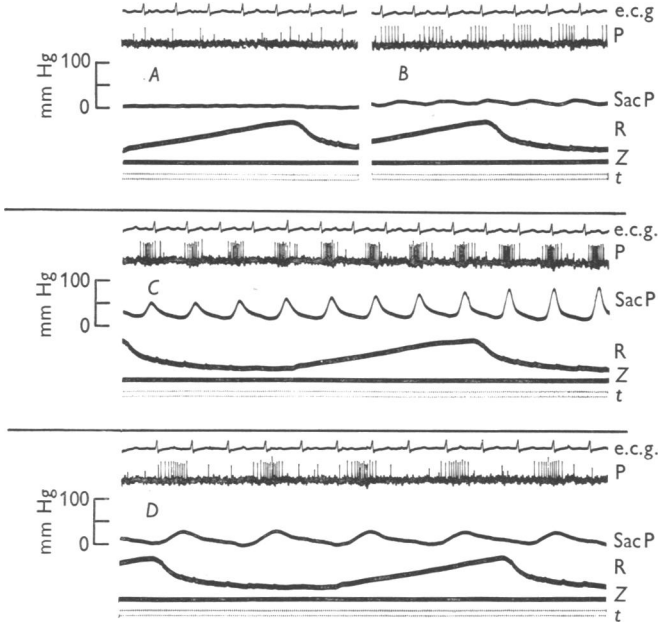

Fig. 6. Impulse activity recorded from the afferent fibre (right vagus) of a baroreceptor in the pulmonary arterial sac, before (*A*) and during (*B*, *C* and *D*) pulsatile distension of the sac (132 pulsations/min in *B* and *C*; 60/min in *D*). Note that impulse activity in *B*, *C* and *D* is synchronous with the pressure pulsations in the sac and not with the animal's heart beat. In this and Fig. 7 the following abbreviations are used: e.c.g., electrocardiogram; P, action potentials recorded from vagal slip; Sac P, pressure in pulmonary arterial sac (mm Hg); R, tracheal pressure (upstroke representing inflation); Z, zero reference line for sac pressure optical manometer; *t*, time marker 1/50 sec.

Action potentials were also recorded to determine whether distension of the sac caused distortion of the overlying aortic arch sufficient to activate the aortic baroreceptors. Recordings were made from 25 aortic baroreceptor fibres: none of these was activated directly by distension of the sac. Thus, in Fig. 7*A*, *B* distension with a pressure of 125/20 mm Hg produced a small rise in mean systemic pressure (from 92 to 100 mm Hg) accompanied by a slight increase in aortic baroreceptor activity. It should be noted that, in this case, impulse activity was synchronous with ventri-

cular systole (as judged by the e.c.g.) and not with the applied pressure changes in the sac.

Similarly there was no evidence that right or left atrial receptors were stimulated directly by distension of the sac. In the experiment depicted in Fig. 7*C*, *D* impulse activity was in time with the animal's heart beat and appeared to be unaffected by the large pressure excursions in the sac, even though this receptor was situated immediately in front of the sac at the junction of superior vena cava and right atrium.

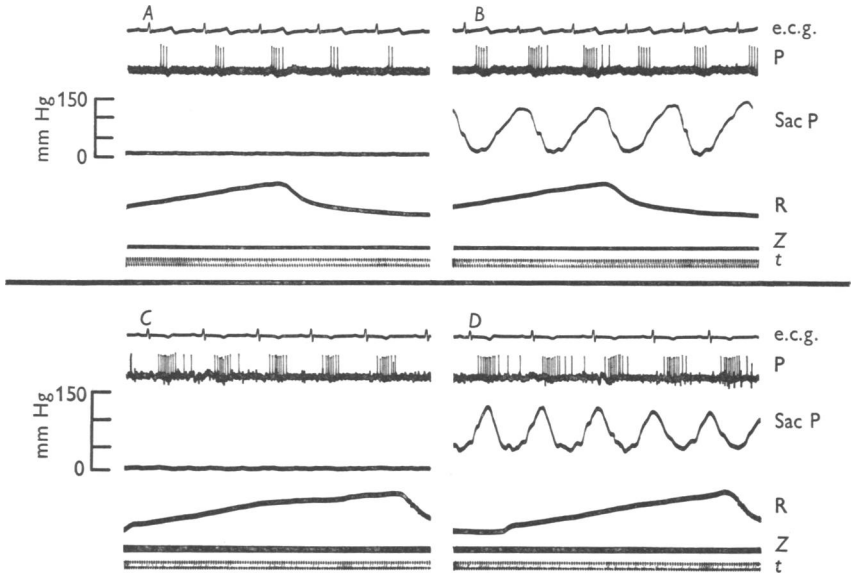

Fig. 7. *A*, *B*, impulse activity from an aortic baroreceptor (left vagus) before (*A*) and during (*B*) pulsatile distension of the sac. Mean femoral arterial pressure was measured by a Hg manometer (*A*, 92 mm Hg; *B*, 100 mm Hg). This was an unusually small increase in systemic pressure to be evoked by gross distension of the sac, probably because the left vagus nerve had been partially dissected to record action potentials. *C*, *D*, impulse activity from a right atrial receptor (right vagus) before (*C*) and during (*D*) distension of the sac. Note that impulse activity was related to the animal's heart beat and not to the pressure pulse in the sac. In *C* and *D* some of the spikes have been retouched to aid reproduction. Abbreviations as in Fig. 6.

DISCUSSION

Histological evidence has been available for many years that the pulmonary artery is supplied with afferent vagal fibres which terminate in endings of the baroreceptor type (for references, see Coleridge *et al.* 1961). Recently electrophysiological techniques have shown that the activity of these receptors is determined by the pressure within the vessel (Bianconi & Green, 1959; Coleridge & Kidd, 1961*a*). Less is known about remote effects produced by stimulation of these endings.

There is evidence that reflex cardiovascular and respiratory effects can be produced by alterations in pressure in the pulmonary circulation (Churchill & Cope, 1929; Harrison, Calhoun, Cullen, Wilkins & Pilcher, 1932; Schwiegk, 1935; Schweitzer, 1936; Parin, 1947). Although later work suggested that these effects were elicited mainly from the venous side of the pulmonary circuit (Daly, Ludány, Todd & Verney, 1937; Aviado, Li, Kalow, Schmidt, Turnbull, Peskin, Hess & Weiss, 1951; Downing, 1957), interpretation of many of these experiments is difficult because the applied pressure changes undoubtedly affected both intra- and extrapulmonary vessels, and sometimes even the chambers of the heart. To be convincing, evidence as to reflex effects initiated by stimulation of pulmonary arterial baroreceptors must be obtained from experiments in which the applied stimulus is confined to the extrapulmonary part of the vessel itself.

This was achieved in the present experiments by distending an isolated segment of the pulmonary artery in which there are known to be baroreceptors. In general, the effects fell into two main groups. Distension with pulsatile pressures around a mean of up to 60 mm Hg produced either no change or a fall in systemic pressure (group 1); distension with higher pressures (mean greater than 80 mm Hg) produced a rise in systemic pressure accompanied by vigorous respiratory movements (group 2). While both group 1 and 2 responses were abolished by vagotomy, only the group 1 response was abolished by cooling the cervical vagi to 7° C. A somewhat similar pattern of results was observed in the few experiments in which the right pulmonary artery was distended with a balloon: distension with smaller volumes tended to produce either no change or a fall in pressure, whereas distension with larger volumes produced a rise.

A comparable grouping of effects was noted by Osorio & Russek (1962) when the main branches of the pulmonary artery of dogs were distended with a balloon or a cuffed cylinder. In response to what they described as 'weaker' distension they observed either no change or a fall in systemic pressure, whereas 'stronger' distension caused a rise. The effect of vagotomy was unfortunately not recorded. They also reported that both grades of distension caused an increase in pulmonary arterial pressure which was thought to be reflex in origin, although not abolished by vagotomy.

Systemic hypertension was also reported by Lewin, Cross, Rieben & Salisbury (1961) following distension of the main pulmonary trunk while the greater and lesser circulations were perfused at constant flow. The effect was abolished by cutting or cooling (temperature unspecified) the vagus nerves. They concluded that the response was due to vasomotor changes because systemic flow was constant. It is of considerable interest

to note, once more, that systemic hypertension followed gross distension of the pulmonary artery, the vessel being distended with a balloon containing 18–28 ml. air or with blood at a pressure of 80–200 mm Hg.

In seeking explanations for the fall in systemic pressure it seems unlikely, in view of the observed changes in atrial pressure, that the hypotension was due to obstruction of flow through adjacent vessels by pressure of the distended sac. In this connexion, moreover, while distension with a pressure as low as 20–25 mm Hg could cause hypotension with vagi intact (Fig. 3*D*), after vagotomy distension with pressures greater than 100 mm Hg never produced a fall in pressure. There was no evidence that adventitious stimulation of adjacent aortic or atrial receptors played any part in eliciting the response. Since the systemic hypotension was produced by distending that part of the vessel beyond the bifurcation, where there are known to be baroreceptors, since those receptors were shown to be activated by the pressures employed to distend the sac, and since the response was abolished by cooling the vagus nerves to 7–8° C (at which temperature conduction in pulmonary baroreceptor fibres is blocked, Coleridge *et al.* 1961) it seems reasonable to conclude that the effect was mediated by the pulmonary arterial baroreceptors.

In addition, distension of the sac with low pressures occasionally evoked a brief and inconstant bradycardia. Although the small number of experiments showing this effect precluded systematic investigation, we think it likely that this response was also mediated by the pulmonary arterial receptors. In this connexion Aviado *et al.* (1951), employing a technique of varying pressures in different parts of the pulmonary circulation, claim to have shown that receptors exist in the pulmonary trunk whose stimulation results in bradycardia. Nevertheless, their claim has been criticized by Heymans & Neil (1958), who point out that it was not substantiated by their experimental records.

The mechanism of the systemic hypertension elicited by marked distension of the pulmonary artery (Lewin *et al.* 1961; Osorio & Russek, 1962; present authors) has yet to be determined. Although abolished by vagotomy, it was still present after the vagus nerves had been cooled to 7° C. This hypertensive response (accompanied in our experiments by active respiratory movements) must, therefore, have been due to the operation of some mechanism other than the pulmonary baroreceptors. In this regard, Lewin *et al.* (1961) emphasize that their responses were obtained from distension of the main trunk alone. This, they claim, confirms the finding which they (quite wrongly) attribute to the present authors (Coleridge & Kidd, 1960), that baroreceptors are not to be found beyond the bifurcation. On the contrary, and on this the evidence is unequivocal, apart from a few endings near the valves the main trunk is

devoid of receptors: the great majority are situated at or beyond the bifurcation (Coleridge *et al.* 1961).

Thus the results of the present experiments suggest that progressive distension of the pulmonary artery evokes two opposing reflex mechanisms, both dependent upon intact vagus nerves. Distension with pressures up to about 60 mm Hg causes systemic hypotension (and occasionally bradycardia) mediated by the pulmonary arterial baroreceptors. With further increase in distension, despite augmentation of pulmonary baroreceptor discharge, a reversal of response occurs and systemic pressure rises. Thus the inhibitory effect of the baroreceptors has been overcome by a more powerful pressor response. It remains to be seen whether the afferent endings subserving this latter effect are situated in the wall of the pulmonary artery or elsewhere.

SUMMARY

1. A preparation is described in which the reflex effects of stimulating baroreceptors in the pulmonary artery have been investigated. In anaesthetized dogs the right pulmonary artery, with nerve supply intact, was converted into a closed sac which could be distended by a balloon or by blood at measured pressures. Only the left lung was ventilated and it received the whole output of the right ventricle.

2. In eight out of eighteen dogs pulsatile distension of the sac (mean pressure between 20 and 60 mm Hg) produced systemic hypotension and sometimes bradycardia; in ten dogs there was little or no effect. Effects were augmented by carotid occlusion and abolished by cooling (7–8° C) or section of the vagus nerves.

3. Pulsatile distension of the sac with higher pressures (mean pressure greater than 80 mm Hg) caused systemic hypertension and respiratory movements of the chest wall and diaphragm. These effects were abolished by vagotomy, but not by cooling the vagus nerves to 7–8° C.

4. Potentials recorded from afferent vagal fibres showed increased activity of baroreceptors in the pulmonary arterial sac during distension. Receptors in the adjacent aortic arch and atria were not directly stimulated by distension of the sac.

5. It is concluded that the hypotension was reflexly brought about by activation of the pulmonary arterial baroreceptors. The mechanism of the hypertensive response has yet to be determined.

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